Therapeutic application of transcranial magnetic stimulation in Parkinson’s disease: The contribution of expectation

Antonio P. Strafella,a,* Ji Hyun Ko,a and Oury Monchib

aMontreal Neurological Institute, Neurology and Neurosurgery Dept., McGill University, 3801 University St., Montréal, QC, Canada H3A 2B4
bFunctional Neuroimaging Unit, Geriatric’s Institute, University of Montréal, Montréal, Québec, Canada

Received 7 December 2005; revised 30 January 2006; accepted 3 February 2006
Available online 20 March 2006

Repetitive transcranial magnetic stimulation (rTMS) is a valuable probe of brain function. Ever since its adoption as a research tool, there has been great interest regarding its potential clinical role. Presently, it is unclear whether rTMS will have some role as an alternative treatment for neuropsychiatric and neurological disorders such as Parkinson’s disease (PD). To date, studies addressing the contribution of placebo during rTMS are missing. The placebo effect has been shown to be associated either with release of dopamine in the striatum or with changes in brain glucose metabolism. The main objective of this study was to test whether, in patients with PD, the expectation of therapeutic benefit from rTMS, which actually was delivered only as sham rTMS (placebo-rTMS) induced changes in striatal [11C] raclopride binding potentials (BP) as measured with positron emission tomography (PET). Placebo-rTMS induced a significant bilateral reduction in [11C] raclopride BP in dorsal and ventral striatum as compared to the baseline condition. This reduction BP is indicative of an increase in dopamine neurotransmission. The changes in [11C] raclopride binding were more evident in the hemisphere contralateral to the more affected side supporting the hypothesis that the more severe the symptoms, the greater the drive for symptom relief, and therefore the placebo response. This is the first study addressing the placebo contribution during rTMS. While our results seem to confirm earlier evidence that expectation induces dopaminergic placebo effects, they also suggest the importance of placebo-controlled studies for future clinical trials involving brain stimulation techniques.

© 2006 Elsevier Inc. All rights reserved.

Keywords: Positron emission tomography; Transcranial magnetic stimulation; Parkinson’s disease; Dopamine; Placebo; Expectation

Introduction

Transcranial magnetic stimulation (TMS) is a valuable probe of brain function that is unparalleled in its ability to alter cortical activity in awake behaving humans. Ever since its adoption as a research tool, there has been great interest regarding its potential clinical role, perhaps due to the intuitive appeal of the idea that non-invasive stimulation of potentially plastic neural circuits may have some application (Wassermann and Lisanby, 2001; Shimamoto et al., 1999; Tsuji and Akamatsu, 2003). Presently, however, it is unclear whether repetitive TMS (rTMS) will have some role as an alternative treatment for neuropsychiatric and neurological disorders such as Parkinson’s disease (PD).

Recently, several studies have suggested the therapeutic efficacy of rTMS in PD (Mally and Stone, 1999a,b; Pascual-Leone et al., 1994; Shimamoto et al., 1999; Siebner et al., 1999; Lomarev et al., 2005) while other studies have found no clinical improvement of motor performance in PD (Ghabra et al., 1999, Leone et al., 1994; Shimamoto et al., 1999; Siebner et al., 1999; Tergau et al., 1999). Although the usefulness of rTMS remains controversial, interest remains high, in light of recent studies in PD demonstrating that stimulation of motor cortex through chronic subdural electrodes may be considered as a valid alternative treatment to deep brain stimulation of the subthalamic nucleus (Canavero et al., 2003; Drouot et al., 2004).

Thus, research into clinical applications for rTMS remains active, but, to date, studies investigating the contribution of placebo are still missing. The placebo effect is not uncommon in trials of therapy for PD and PD patients can present marked and sustained improvements on objective measures with placebo treatment even in rigorously controlled and blinded trials (Goetz et al., 2000).

Expectation seems to play a major role in the placebo effect which has been shown to be associated either with release of dopamine (de la Fuente-Fernandez et al., 2001, 2002a; Kaasinen et al., 2004), changes in brain glucose metabolism (Mayberg et al., 2002; Volkow et al., 2003) or changes in neuronal firing (Benedetti et al., 2004). As for rTMS, it should also be reminded that medical devices enhance the placebo effect (Kaptchuk et al., 2000).

In rTMS, another confounding factor is represented by the TMS-induced sensory experience (e.g. scalp sensation) which could not only enhance indirectly patient’s expectation (Kaptchuk et al., 2000; Tsuji and Akamatsu, 2003) but also induce some dopamine release itself (Nieoullon et al., 1977), thus increasing the contribution of placebo.
Based on these premises, the main objective of this study was to test whether, in patients with PD, the expectation of therapeutic benefit from rTMS, which actually was delivered only as sham rTMS (placebo-rTMS), could be responsible for significant changes in striatal $[^{11}C]$ raclopride binding potentials (BP) as measured with positron emission tomography (PET). The current study may provide insights into the unexplored contribution of some of the confounding elements of rTMS when applied in a clinical setting. In the current study design, we predicted a bilateral and more diffuse release of dopamine involving both the dorsal and ventral striatum which would suggest an involvement of both nigrostriatal and mesolimbic dopaminergic pathways (de la Fuente-Fernandez et al., 2002a). This neuronal network is different from the cortico-striatal activation described, in our previous studies, in healthy subjects (Strafella et al., 2001, 2003) and PD patients (Strafella et al., 2005) in which rTMS induced only a focal release of dopamine in the ipsilateral dorsal striatum.

Methods

Experimental design

Seven patients with moderate PD (Table 1) and no medical history of psychiatric symptoms participated in the study after having given written informed consent. For these experiments, we explicitly avoided selecting patients with a mild form of PD because these patients may not have the same clear response to placebo as those with a more severe form of the disease. PD patients were studied OFF medication after overnight withdrawal (12–18 h) of their antiparkinsonian medications (Langston et al., 1992). They were invited to attend an initial session during which they were fully informed by the same investigator about the rTMS procedure and its potential of providing transitory clinical improvement of PD motor symptoms. They were also made aware that at the end of the PET scan they would be explicitly asked whether or not they had perceived any improvement in their symptoms after the rTMS session, we measured their motor threshold.

Within 2 weeks, each patient underwent two $[^{11}C]$ raclopride PET scans at the same time on two consecutive days, a $[^{11}C]$ raclopride PET (placebo scan) with sham rTMS and a placebo-free baseline scan, performed in an open fashion during which the patients were informed that no rTMS was involved. The scan order was randomized across subjects. None of the patients received any compensation for their participation to the study (i.e. no monetary reward). A debriefing session followed upon completion of the imaging studies. The experiments were approved by the Research Ethics Committee of the Montreal Neurological Institute and Hospital.

Transcranial magnetic stimulation

Repetitive TMS was carried out with a Magstim high-speed magnetic stimulator (Magstim, UK). This device permits delivery of high-frequency magnetic stimuli through the same coil. Sham rTMS was delivered through a 7 cm figure-of-eight focal coil angled at 90° with only the edge of the coil resting on the scalp. The coil was held in the scanner in a fixed position by a mechanical arm over the left motor cortex. Stimulus intensity, expressed as a percentage of the maximum stimulator output, was set only at 30% of their resting motor threshold for the right first dorsal interosseous muscle (FDI). This stimulation intensity along with the tilted arrangement of the figure-of-eight focal coil, while ineffective in inducing any cortical activation or unpleasant sensations (Tofs, 1990; Roth et al., 1991; Rothwell, 1997; Wassermann and Lisanby, 2001), ensures an adequate noise and scalp sensation. As already described in our previous TMS studies (Strafella et al., 2000, 2001, 2003, 2004, 2005), the motor threshold was defined as the lowest stimulus intensity able to elicit, from the FDI, 5 motor evoked potentials (MEPs) of at least 50 μV amplitude in a series of 10 stimuli delivered over the MC at intervals longer than 5 s. MEPs were recorded with Ag/Cl surface electrodes fixed on the skin with a belly-tendon montage. Electromyogram (EMG) signal was filtered (50–50 kHz band-pass) and displayed on the EMGrapher screen (Keypoint, Medtronic, Canada). Motor thresholds were measured on 2 different occasions, during the initial informative session and just before the PET placebo scan. Before the placebo acquisition scan, six rTMS blocks were delivered, each block separated by a 5-min interval. In each block, 20 10-pulse trains were delivered at a stimulation frequency of 5 Hz, with a between-train

Table 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Hoen–Yahrstage</th>
<th>UPDRS (III) OFF medication</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>2</td>
<td>24</td>
<td>Levodopa, 300 mg/day</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>3</td>
<td>28</td>
<td>Pramipexole, 0.75 mg/day</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>3</td>
<td>27</td>
<td>Levodopa, 300 mg/day</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>2</td>
<td>19</td>
<td>Pramipexole, 1.0 mg/day</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>2</td>
<td>20</td>
<td>Levodopa, 400 mg/day</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>3</td>
<td>30</td>
<td>Levodopa, 300 mg/day</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>2</td>
<td>20</td>
<td>Pramipexole, 1.5 mg/day</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>60.4 (±4.86)</td>
<td>2.4 (±0.49)</td>
<td>24 (±4.1)</td>
<td>Levodopa, 380 mg (±116.6)</td>
</tr>
</tbody>
</table>

(UPDRS III): Unified Parkinson’s Disease Rating Scale, motor section.
interval of 5 s. rTMS did not induce any EMG responses in the relaxed FDI, abductor pollicis brevis or extensor digitorum communis.

Subjective ratings

Following the placebo scan, subjects were asked whether or not they had perceived any improvement in their symptoms after the rTMS procedure. They rated this improvement on an arbitrary scale from 0 to 3 (0 = no improvement, 1 = mild, 2 = moderate, 3 = excellent). We explicitly avoided, following rTMS, to assess changes in motor functions using more objective tests (i.e. unified Parkinson’s disease rating scale), because such interventions could degrade the scans with motion artifacts, and movement itself has been shown to induce striatal release of dopamine (Ouchi et al., 2002; Goerendt et al., 2003).

Positron emission tomography and imaging analysis

PET scans were obtained with a CTI/Siemens HR plus tomograph operating in 3D mode, yielding images of resolution 4.2 mm full-width at half maximum. Within 5 min of the end of the rTMS session, 10 mCi of [11C] raclopride was injected into the left antecubital vein over 60 s and emission data were then acquired over a period of 60 min in 26 frames of progressively increasing duration. After the emission scan, a 10 min transmission scan was performed with a rotating radioactive source (68Ga) for attenuation correction.

A high-resolution MRI (Siemens Sonata 1.5 T; T1-weighted images, 1 mm slice thickness) of each subject’s brain was acquired and transformed into standardized stereotaxic space (Talairach and Tournoux, 1988) using automated feature-matching to the MNI template (Collins et al., 1994).

PET frames were summed, registered to the corresponding MRI (Woods et al., 1993) and transformed into standardized stereotaxic space using the transformation parameters previously determined for the MRI. Voxelwise [11C] raclopride BP was calculated using a simplified reference tissue (cerebellum) method (Lammertsma and Hume, 1996; Gunn et al., 1997) to generate statistical parametric images of change in BP (Aston et al., 2000). This method uses the residuals of the least-squares fit of the compartmental model to the data at each voxel to estimate the standard deviation of the BP estimate, thus greatly increasing degrees of freedom. Only peaks falling within the striatum were considered. A reduction in [11C]raclopride BP is indicative of an increase in extra-cellular dopamine concentration (Dewey et al., 1993; Laruelle et al., 1997; Endres et al., 1997; Breier et al., 1997). For the purpose of the group analysis, PET images were flipped along the horizontal axis so that the hemisphere contralateral to the more affected body side (i.e. more affected hemisphere) was set on the left while the less affected hemisphere was displayed on the right.

A threshold level of \( t \geq 4.1 \) was considered significant \((P < 0.05, 2\text{-}tailed)\) corrected for multiple comparisons (Worsley et al., 1996), assuming a search volume equal to the entire striatum, an effective image filter of 6 mm FWHM and 276 degrees of freedom (Aston et al., 2000). In each subject, BP values from the dorsal and ventral striatum (Haber and McFarland, 1999; Mawlawi et al., 2001; Martinez et al., 2003) were extracted with regions of interest (ROI) drawn on the MRI at the level of the

---

Fig. 1. Placebo rTMS-induced dopamine release: axial, coronal and sagittal sections of the statistical parametric map of the change in [11C] raclopride BP, overlaid upon the average MRI of all subjects in stereotaxic space, at the level of the dorsal (A) and ventral (B) striatum. The left and right hemispheres display, respectively, the more affected and less affected side.
Results

Placebo rTMS induced a significant bilateral reduction in $[^{11}C]$ raclopride BP in dorsal and ventral striatum as compared with the baseline condition (Fig. 1).

In the more affected hemisphere, placebo rTMS induced 11.8% decrease in $[^{11}C]$ raclopride BP in the caudate (ROI: mean ± SD, baseline: 2.040 ± 0.34, placebo: 1.799 ± 0.30; $P = 0.001$), 13.4% in the putamen (ROI: mean ± SD, baseline: 2.401 ± 0.40, placebo: 2.078 ± 0.39; $P = 0.001$) and 11.1% in the ventral striatum (ROI: mean ± SD, baseline: 1.928 ± 0.21, placebo: 1.713 ± 0.19; $P < 0.001$) (Figs. 2, 3). The change in $[^{11}C]$ raclopride binding in the less affected hemisphere, although less remarkable, was in the order of 8.6% for caudate (ROI: mean ± SD, baseline: 2.124 ± 0.19, placebo: 1.940 ± 0.22; $P = 0.003$), 9.0% for the putamen (ROI: mean ± SD, baseline: 2.161 ± 0.22, placebo: 1.967 ± 0.29; $P = 0.02$) and 7.9% for the ventral striatum (ROI: mean ± SD, baseline: 1.932 ± 0.35, placebo: 1.778 ± 0.22; $P = 0.03$).

Voxel-based analysis revealed that the magnitude of change in $[^{11}C]$ raclopride binding was greater in the dorsal and ventral striatum of the more affected hemisphere as compared to the less affected hemisphere (Fig. 1); however, this difference reached a statistical significance only for the putamen ($P = 0.03$) (Fig. 4, top). The significant cluster of change in $[^{11}C]$ raclopride BP of the dorsal striatum in the more affected hemisphere was 34.5% greater than its contralateral region, in the less affected hemisphere. Such a difference in cluster was in the order of 10.2% for the ventral striatum (Fig. 4, bottom).

Clinically, four PD patients described a mild to moderate clinical improvement (mean ± SD, 2.3 ± 0.97) while three patients reported no clinical benefit following placebo rTMS. A statistical analysis was conducted to test whether any differences existed in $[^{11}C]$ raclopride BP either in the dorsal or ventral striatum between these two groups of patients. The patients who perceived the clinical benefit had a slight higher amount of dopamine release in the dorsal striatum (putamen, caudate nucleus), but this difference failed to reach statistical significance (Fig. 5). Similarly, no difference was observed in the ventral striatum.

Discussion

The present study confirms earlier evidence of a diffuse striatal dopamine release in PD in response to placebo (de la Fuente-Fernandez et al., 2001, 2002a). While the expectation of therapeutic benefit from rTMS certainly played a major role in this effect, a possible contribution from TMS-induced sensory experience is also very likely. The latter, indeed, either by...
increasing, indirectly, patient’s expectation (Kaptchuk et al., 2000; Tsuji and Akamatsu, 2003) or by inducing some dopamine release itself (Nieuillon et al., 1977) could have enhanced the placebo contribution.

The neuroanatomical localization of our findings suggests that placebo rTMS is able to activate in PD patients the same brain network activated by other placebo and active dopaminergic drugs (de la Fuente-Fernandez et al., 2001), thus supporting the notion of a shared neuronal network (Petrovic et al., 2002). The bilateral changes in \(^{11}\)C raclopride BP involving the dorsal and ventral striatum suggest that both nigrostriatal and mesolimbic dopaminergic pathways were involved in placebo-rTMS. This striatal neuronal network is different from the cortico-striatal activation described, in our previous studies, in healthy subjects (Strafella et al., 2001, 2003) and in PD patients (Strafella et al., 2005) in which rTMS induced only a focal release of dopamine in the ipsilateral dorsal striatum.

In the present study, the bilateral striatal reduction in BP ranged from 7.9% to 13.4%; this is greater than the reported 7% test–retest reliability of this method (Wang et al., 1999).

While placebo-rTMS induced in all patients a significant biochemical response in the striatum (Fig. 3), only four PD patients perceived a certain degree of clinical benefit. This discrepancy is not a novel finding and has also been reported, previously, in placebo studies involving either caffeine (Kaasinen et al., 2004) or apomorphine (de la Fuente-Fernandez et al., 2001, 2002a). It has been suggested that the possible role of dopamine in mediating expectation and coding uncertainty could be crucial for this phenomenon (de la Fuente-Fernandez and Stoessl, 2002; de la Fuente-Fernandez et al., 2004; Kaasinen et al., 2004; Fiorillo et al., 2003). Indeed, dopamine neurons have long been implicated with reward mechanisms, involving either expectation of reward (tonic activation) or reward itself (phasic activation) (Wise and Rompre, 1989; Schultz, 1998; Fiorillo et al., 2003). In addition, dopaminergic neurons have also been shown to specifically code uncertainty, and the level of sustained dopaminergic activity is highest when uncertainty is highest (i.e. 50% chance of receiving active/placebo treatment) (Fiorillo et al., 2003). Therefore, the higher the probability of reward (i.e. clinical benefit), the greater the expectation and consequently the placebo effect (de la Fuente-Fernandez et al., 2004). Thus, in our study, the expectation of a clinical benefit along with the uncertainty of receiving treatment (active vs. placebo rTMS) may have played a significant contribution to the striatal biochemical response.

Previous reports have shown that the degree of placebo-induced dopamine release in the dorsal striatum seems to be related to the degree of perceived improvement by the patient (de la Fuente-Fernandez et al., 2001) while placebo induces a similar amount of dopamine release in the ventral striatum regardless of the degree of perceived improvement (de la Fuente-Fernandez et al., 2002a). In our study, while our findings were consistent with those reports with regard to the ventral striatum, we did not observe significant differences in \(^{11}\)C raclopride BP in the dorsal striatum between the group of patients who perceived the clinical benefit and the group who did not. A number of reasons could explain this difference. The first explanation could be simply the small number of patients or the confounding factor represented by the TMS-induced sensory experience which could also have contributed to some dopamine release. However, other factors could also be involved. Indeed, differences in the magnitude of the placebo response are not unknown among different clinical trials in PD (Shetty et al., 1999; Goetz et al., 2000; Freed et al., 2001). These differences in magnitude have been described to be in relation to either differences in patient group characteristics, amount of information provided or previous medication exposure, all of which could influence the amount of expectation and therefore the perception of clinical benefit (de la Fuente-Fernandez and Stoessl, 2002; de la Fuente-Fernandez et al., 2002b). All these factors could also have played a role in the observed lack of difference in \(^{11}\)C raclopride BP in the dorsal striatum between our two groups of patients.

An interesting observation was represented by the fact that changes in \(^{11}\)C raclopride binding were clearly more evident in the hemisphere contralateral to the more affected side (Fig. 4). This asymmetry seems to support the hypothesis that the more severe the symptoms the greater the drive for symptom relief and therefore the placebo response. It is worth noting that a larger cluster of change in binding in the more affected hemisphere was also observed in our previous rTMS study involving PD patients (Strafella et al., 2005). We claimed that because of the more advanced loss of re-uptake sites released dopamine diffuses out to more distant regions and possibly interacts with larger areas of the receptor population in the dopamine-denervated striatum (Zigmond et al., 1990). Thus, it cannot be excluded that this could also play a role in our present study.

It should be noted that a reduction in BP was also observed in the thalamus (Fig. 1), which was similar to what it has also been described in previous placebo studies involving expectation (Kaasinen et al., 2004).

To date, it is unclear whether rTMS could have some role as alternative treatment for neuropsychiatric and neurological disorders. This study was designed to provide some insights into the unexplored contribution of some of the confounding elements (i.e. expectation, sensory experience) of rTMS when applied in a clinical setting, and it has clearly demonstrated the importance of placebo-controlled studies for future clinical trials involving brain stimulation techniques. Indeed, the placebo rTMS-induced changes in brain dopaminergic neurotransmission similar to the one activated also by other placebo and active dopaminergic drugs (de la Fuente-Fernandez et al., 2001) seem to support the notion of a shared neuronal network (Petrovic et al., 2002).

Acknowledgments

We wish to thank the staff of the McConnell Brain Imaging and Medical Cyclotron Units for their assistance. This work was funded by the Canadian Institutes of Health Research, the Fonds de la Recherche en Santé du Québec and the Canada Foundation for Innovation to APS.

References


